Advances in Therapies and Imaging for Systemic Vasculitis

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Advances in Therapies and Imaging for Systemic Vasculitis

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***Abstract*—**Vasculitis is a systemic disease characterized by immune-mediated injury of blood vessels. Current treatments for vasculitis, such as glucocorticoids and alkylating agents, are associated with significant side effects. Furthermore, the management of both small and large vessel vasculitis is challenging because of a lack of robust markers of disease activity. Recent research has advanced our understanding of the pathogenesis of both small and large vessel vasculitis, and this has led to the development of novel biologic therapies capable of targeting key cytokine and cellular effectors of the inflammatory cascade. In parallel, a diverse range of imaging modalities with the potential to monitor vessel inflammation are emerging. Continued expansion of combined structural and molecular imaging using positron emission tomography with computed tomography or magnetic resonance imaging may soon provide reliable longitudinal tracking of vascular inflammation. In addition, the emergence of radiotracers able to assess macrophage activation and immune checkpoint activity represents an exciting new frontier in imaging vascular inflammation. In the near future, these advances will allow more precise imaging of disease activity enabling clinicians to offer more targeted and individualized patient management. **(*Arterioscler Thromb Vasc Biol*. 2019;39:00-00. DOI: 10.1161/ATVBAHA.118.310957.)**

Key Words: antibodies, antineutrophil cytoplasmic ■ biological products ■ giant cell arteritis ■ inflammation ■ positron emission tomography

Primary systemic vasculitides are an uncommon group of diseases characterized by relapsing and remitting immune-mediated inflammation of blood vessels. They affect patients of all ages and pose unique diagnostic and therapeutic challenges. Systemic vasculitis can be broadly defined by the size of the affected vessels into small vessel vasculitis (SVV), medium vessel vasculitis (MVV), and large vessel vasculitis (LVV) with some overlap.[1] In LVV, the inflammatory response begins at the adventitia and spreads inward toward medial and intimal layers.[2] This results in the development of occlusive and aneurysmal vascular lesions. In contrast, small vessel inflammation typically begins with endothelial injury and intimal inflammation, which propagates outward to the media and adventitia.[3] Further spread to the adventitia results in a panarteritis, although this is more typical of MVV, which shares features of both.[4] The early inflammatory injury of the intima with subsequent activation of the coagulation cascade in small caliber vessels explains the thrombotic and necrotizing pathology that characterizes SVV.

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Although effective, current treatments for systemic vasculitis are associated with significant morbidity,[5] and survival remains poor with many patients experiencing chronic relapsing systemic inflammation that contributes to the development and progression of cardiovascular disease.[6,7] Indeed, ≈15% of patients experience a major adverse cardiovascular event within 5 years of diagnosis.[6,7] Identifying vasculitis early, assessing response to therapy, and detecting disease relapse remain important clinical challenges. The last decade has seen major advances in our understanding of the pathogenesis of vasculitis. These discoveries have led to the development of novel treatments, which seek to provide greater efficacy and a more acceptable side effect profile. In this review, we discuss the recent advances in understanding disease mechanisms of the major vasculitides in adults, the consequent development of new treatments, and how existing and novel imaging techniques may be used to improve diagnosis and disease monitoring.

Large Vessel Vasculitis

Clinical Context and Challenges

LVV is the most common primary systemic vasculitis[8,9] and includes giant cell arteritis (GCA) and Takayasu arteritis (TA). The central feature of both is granulomatous arteritis that involves the aorta and its major branches.[2] GCA exclusively

Received on: December 3, 2018; final version accepted on: May 20, 2019.

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Nonstandard Abbreviations and Acronyms

ADA2	adenosine deaminase 2
ANCA	antineutrophil cytoplasmic antibody
BAFF	B-cell activating factor
BlyS	B-lymphocyte stimulator
C5aR	C5a receptor
CRP	C-reactive protein
CT	computed tomography
CTA	computed tomographic angiography
EGPA	eosinophilic granulomatosis with polyangiitis
ET-1	endothelin-1
ET_A	endothelin-A
ET_B	endothelin-B
Ga-DOTATATE	gallium-68-labeled [1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid]-D-Phe1, Tyr3-octreotate
GCA	giant cell arteritis
GiACTA	giant cell arteritis actemra
GLUT	glucose transporter
GPA	granulomatosis with polyangiitis
IFN-γ	interferon-γ
IL	interleukin
LVV	large vessel vasculitis
MPO	myeloperoxidase
MR	magnetic resonance
MRA	magnetic resonance angiography
MVV	medium vessel vasculitis
PAN	polyarteritis nodosa
PD-1	programmed death-1
PD-L1	programmed death ligand-1
PET	positron emission tomography
PR3	proteinase-3
SST-2	somatostatin receptor subtype 2
SVV	small vessel vasculitis
TA	Takayasu's arteritis
TNFα	tumor necrosis factor-α
TSPO	translocator protein
VSMC	vascular smooth muscle cell

affects individuals aged >50 years with a female-to-male predominance of 3:1. Additionally, GCA is more common in patients of North European descent with an incidence of 20 to 30 per 100 000 people but is uncommon in Asian ethnic groups, incidence ≈1.5 per 100 000.[10,11] It typically affects the branches of carotid, vertebral, and temporal arteries resulting in the classical symptoms of headache, jaw claudication, and loss of vision.[1] Large vessel GCA involvement is increasingly recognized in ≤70% to 80% of patients with GCA and is associated with an increased mortality risk related, in part, to aneurysm formation and dissection.[12] In contrast, TA primarily affects females <50 years of age, has a worldwide incidence of ≈0.8 per million, and is rare in North Europe but is more common in South East Asia.[11,13,14] TA typically involves the aorta and its primary branches leading to vascular occlusion with claudication, aneurysm formation, aortic insufficiency, and cardiac failure.[1]

LVV is a chronic, relapsing disease with ≈80% of patients with GCA[15] and ≈50% of patients with TA[16] experiencing a relapse within 5 years of diagnosis. Current treatment is heavily reliant on prolonged use of glucocorticoids, which is associated with infections, osteoporotic fractures, hypertension, weight gain, and diabetes mellitus.[17] The limited success of steroid-sparing agents such as methotrexate[18] and azathioprine[19] in clinical trials of GCA has reinforced this dependence. In contrast to SVV, LVV lacks validated markers of disease activity to guide immunosuppression and detect subclinical progressive disease. This chronic, relapsing low-grade systemic inflammation contributes to the development of cardiovascular disease, which is a major source of morbidity and mortality.[6,20,21]

Novel Mechanisms, Novel Treatments

Targeting Leucocyte-Cytokine Signatures in LVV

Vascular inflammation in LVV is characterized by 2 distinct leucocyte-cytokine signatures (Figure 1). The IL (interleukin)-6/Th17 cell/IL-17 signature is a key mediator of the early inflammatory response within the vessel wall and is glucocorticoid sensitive. A separate IL-12/Th1 cell/IFN-γ (interferon-γ) pathway promotes sustained granulomatous inflammation and vascular smooth muscle cell (VSMC) proliferation and appears glucocorticoid resistant in GCA.[22]

These concepts are supported by clinical studies showing elevated circulating IL-6, IL-12, and IL-17[23] during active GCA alongside increased Th17/IL-17 and Th1/IFNγ expression in culprit lesions on temporal artery biopsy.[24,25] Following glucocorticoid treatment, circulating IL-6 and IL-17, as well as vessel Th17/IL-17 expression, fall mirroring clinical improvement.[20] However, circulating IL-12 concentrations and tissue Th1/IFNγ expression remain unchanged.[24] Relative tissue expression of these leucocyte-cytokine signatures may influence outcomes as greater culprit lesion expression of IL-17 has been shown to predict an earlier response to glucocorticoids, likelihood of glucocorticoid discontinuation, and a lower risk of relapse.[25] Extrapolating these concepts to TA should be done with caution as recent data show that, despite similar cytokine signatures, glucocorticoids had little effect on IL-17 but suppressed IFNγ.[26] Reasons for this are unclear but may be because of differences in typical affected age group, ethnicity, and genetic associations between TA and GCA.

Targeting IL-6

IL-6 is a potent mediator of the inflammatory response in both the vessel wall and the systemic circulation. Tocilizumab is a humanized monoclonal antibody that competitively inhibits its IL-6 by binding to circulating and membrane-bound IL-6 receptors. The first study of tocilizumab in GCA was published in 2016. This single-center, randomized, placebo-controlled double-blind study enrolled 30 patients, most with new-onset GCA.[27] Patients received monthly tocilizumab or placebo alongside tapered glucocorticoids. The primary outcome of complete remission by 12 weeks was achieved by 17 (85%) patients in the tocilizumab arm compared with 4 (40%) patients in the placebo arm. Tocilizumab was also associated with a greater relapse-free survival at 1 year, longer

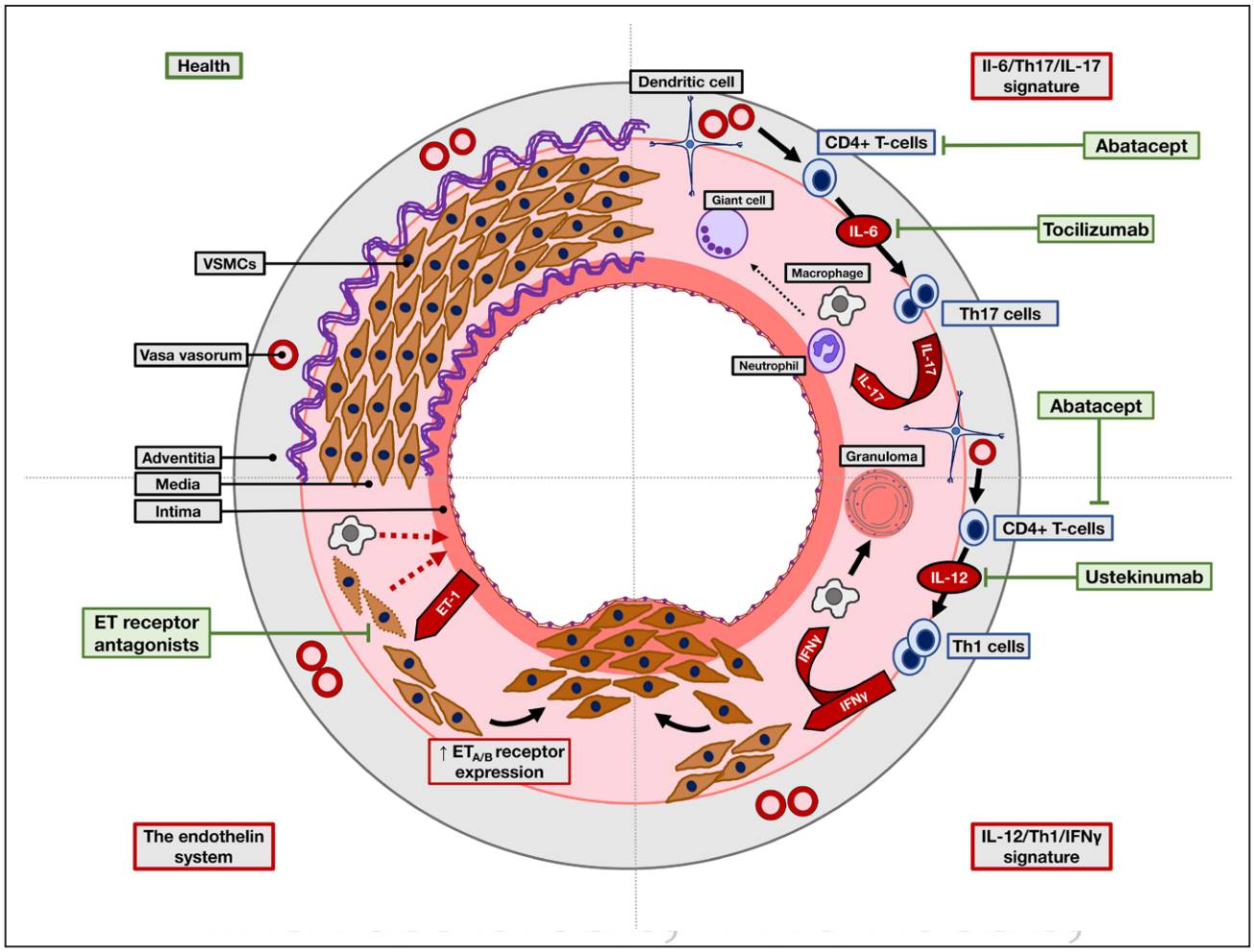

Figure 1. Targeting key mechanisms in the pathogenesis of large vessel vasculitis (LVV). Cross-sectional diagram of a large vessel depicting important pathogenic pathways of vasculitis. **Upper left** shows vessel structure in health; **upper right** shows the IL (interleukin)-6/Th17 cell/IL-17 pathway; **lower right** shows IL-12/Th1 cell/IFNγ (interferon-γ) pathway; **lower left** shows the ET-1 (endothelin-1) system. Adventitial dendritic cells are activated by an as yet unknown trigger, leading to monocyte, $CD4^+$, and $CD8^+$ T-cell infiltration via the vasa vasorum. Cellular infiltration stimulates the release of several proinflammatory cytokines including IL-6 and IL-12. IL-6 induces $CD4^+$ T-cell differentiation toward a Th17 phenotype. These Th17 cells secrete IL-17, which in turn recruits monocytes and neutrophils to the inflamed medial layer. The ensuing florid inflammatory response spreads from the adventitia toward the intima with giant cell formation. Glucocorticoids can effectively suppress this pathway, but more precise targeting of IL-6 is possible by the monoclonal antibody tocilizumab. In parallel, IL-12 promotes polarization of $CD4^+$ to a Th1-IFNγ secreting phenotype. IFNγ release orchestrates macrophage recruitment and granuloma formation, as well as triggering pathways that lead to proliferation and inward migration of vascular smooth muscle cells (VSMCs). This pathway is resistant to suppression by glucocorticoids but can be inhibited by ustekinumab. The widespread uncontrolled T-cell activation can be targeted by abatacept, which blocks T-cell interaction with antigen presenting cells. The inflammatory milieu within the vessel wall causes upregulation of ET-1 at the protein level and increased VSMC ET receptor expression. ET-1 promotes VSMC proliferation and migration that in combination with the effects of IFNγ results in intimal hyperplasia and luminal stenosis characteristic of LVV. In vitro data suggest this may be ameliorated by ET receptor antagonism.

time to first relapse and lower cumulative glucocorticoid dose. Adverse advents were similar between arms.

These findings were extended by the phase 3 GiACTA trial (Giant Cell Arteritis Actemra) that enrolled 251 patients with new-onset, relapsing, or refractory GCA.[28] Randomization was to one of tocilizumab weekly plus 26-week glucocorticoid taper, tocilizumab every 2 weeks plus 26-week glucocorticoid taper, placebo plus 26-week glucocorticoid taper, or placebo plus 52-week glucocorticoid taper. The primary outcome of sustained remission at 52 weeks was met by >50% of patients in the tocilizumab arms demonstrating superiority to placebo (≈15%).[28] Tocilizumab was also associated with lower rates of disease flares, longer time to flare, and a lower cumulative glucocorticoid dose. There was no difference in total adverse events across the 4 groups, and the highest number of serious adverse events occurred in the slow glucocorticoid taper group.[29]

The compelling evidence from these trials led to the approval of tocilizumab for GCA by the Food and Drug Administration in the United States last year and the National Institute for Health and Care Excellence in the United Kingdom this year. The optimal duration of treatment is unclear. This is important given the costs of tocilizumab are ≈$18 000 (≈£12 000) per patient-year. Importantly, from a therapeutic perspective, ≈50% of patients receiving tocilizumab in GiACTA failed to achieve sustained remission at 1 year suggesting that targeting IL-6 alone might be insufficient for adequate disease control in some patients.[28]

A key effect of IL-6 production is the induction of CRP (C-reactive protein) transcription, which drives the

systemic inflammatory response and associated symptoms.[30] Consequently, tocilizumab's inhibition of IL-6 leads to a rapid suppression of circulating CRP, which results in significant symptomatic improvement. This renders CRP ineffective as a marker of disease activity and has raised concerns that tocilizumab may mask ongoing inflammation at the level of the vessel wall. These concerns are supported by clinical trial data. In the GiACTA trial, one patient developed arteritic ischemic optic neuropathy while receiving tocilizumab,[28] and a recent imaging substudy of the first tocilizumab trial by Villiger et al[27] reported that one-third of patients in tocilizumab arm (n=3) had persisting or increased mural contrast enhancement on magnetic resonance angiography (MRA) despite clinical remission.[31] Larger studies particularly with concurrent serial multimodal imaging may help clarify these concerns.

In TA, the first randomized, double-blind, placebo-controlled trial of tocilizumab was published in late 2017.[32] Thirty-six patients aged >12 years with relapsing TA received high-dose glucocorticoids to induce remission before randomization to either tocilizumab or placebo given weekly alongside a tapering glucocorticoid dose. Intention-to-treat analysis failed to demonstrate a clear difference in primary outcomes of time to relapse (P=0.056). The per-protocol analysis did suggest a longer time to relapse in patients receiving tocilizumab (P=0.03) with no increased risk of infections or other serious adverse effects. Further studies are needed to define the role of IL-6 inhibition in TA.

Targeting IL-12 and IL-23

IL-12 and IL-23 induce the polarization of T cells toward INFγ secreting Th1 cells and IL-17 secreting Th17 cells, respectively (Figure 1).[22] IL-12 and IL-23 share a P40 subunit that can be targeted by the novel monoclonal antibody, ustekinumab. Ustekinumab is licensed for use in psoriasis, psoriatic arthritis, and Crohn colitis,[33,34] and data in LVV are emerging. A recent open-label trial recruited 25 patients with refractory GCA and administered ustekinumab at baseline, 1 month, and then 3 months for up to a year.[35] Ustekinumab allowed significant reductions in glucocorticoid dose from a median of 20 to 5 mg, and ≈25% of patients were able to stop glucocorticoids completely within the 12 months after enrollment. Interestingly, in patients who underwent computed tomographic (CT) angiography (CTA) before and after (n=8), all showed an improvement in mural thickness with complete resolution seen in 4 patients.[35] Whether these radiological changes occur because of specific inhibition of Th1/INFγ-mediated VSMC proliferation by ustekinumab or simply by reducing vessel inflammation overall needs clarification. Further randomized trials are now awaited.

Targeting T-Cell Activation

Uncontrolled T-cell activation is a central feature of the inflammatory response in LVV. Abatacept is a fusion protein that inhibits the interaction between CD28 on T cells and CD80 or CD86 on antigen-presenting cells and thus prevents T-cell activation.[36] The clinical benefit of targeting this pathway has recently been assessed by 2 separate randomized controlled trials, one in GCA[37] and the other in TA,[38] with contrasting results. Both trials had a similar design in which all enrolled patients received abatacept over 8 weeks to induce disease remission. Those who achieved remission at 12 weeks after enrollment were randomized 1:1 to either monthly abatacept or placebo. All patients received tapering glucocorticoids from entry, and the primary end point was relapse-free survival at 12 months.[37,38]

In the GCA trial, 41 of 49 (83%) enrolled patients were randomized (ie, achieved remission with abatacept), and relapse-free survival was 48% with abatacept as maintenance therapy compared with 31% with placebo (P=0.049).[37] Patients in the abatacept arm spent ≈10 months in remission compared with ≈4 months with placebo, and there were no differences in infection rates or prednisolone exposure before relapse.[37] However, in the TA trial, the first ever RCT in TA, fewer patients were randomized (26 of 34; 74%), and no difference in relapse-free survival at 12 months was seen between abatacept and placebo (22% versus 40%, respectively).[38] These data provide further support that GCA and TA are distinct, as suggested by their differential geoepidemiology, cytokine profiles, and TA-specific genetic associations.[39] It is worth noting that in the GCA trial ≈50% of patients randomized were new presentations spread equally between treatment arms.[37] In the TA trial, all patients randomized to abatacept had relapsing disease and median disease duration of >5 years compared with <1 year in the placebo arm.[38] Thus, this group likely had difficult-to-control disease and was prone to relapse, which may have influenced achievement of the primary outcome. Regardless, these trials indicate a potential role for abatacept in LVV that warrants additional study.

Imaging of LVV

The diagnosis of GCA often involves tissue biopsy, and performing an interval biopsy to assess disease activity is not feasible. In large vessel GCA and TA, obtaining tissue for diagnosis is frequently impossible. Commonly used circulating measures of disease activity such as CRP and erythrocyte sedimentation rate normalize rapidly after commencement of treatment,[40] despite ongoing inflammation at the level of the vessel[41] and can remain within normal limits even when disease relapses.[42] Furthermore LVV lacks a validated marker of disease activity such as the Birmingham Vasculitis Activity Score in antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis. The potential to visualize and track large vessel inflammation using imaging, therefore, represents an exciting breakthrough in LVV and may yield critical biomarkers of disease activity to guide treatment. In recognition of this, the European League Against Rheumatism released guidance for clinicians on the use of imaging in LVV including technical and operational parameters for ultrasound, CT, magnetic resonance imaging, and positron emission tomography (PET).[43] This guidance also details an extensive future research agenda demonstrating a clear intent to harness the power of multimodal imaging to improve patient outcomes. Table 1 summarizes the current modalities utilized in imaging LVV.

Structural Imaging

Ultrasound

Color doppler ultrasound of the temporal arteries in suspected cranial GCA is a safe, rapidly available, cost-effective

Table 1. Multimodal Imaging of Large Vessel Vasculitis

Modality	Diagnostic Role	Sensitivity	Specificity	Key Imaging Features	Disease Activity Role	Strengths	Weaknesses
US	+	77%	96%	Halo sign	±	Accessible; cost-effective	Operator dependent; unable to detect aortic disease
Cranial MRI	+	73%–93%	81%–88%	Mural thickening; contrast enhancement	ND	Operator independent	Expensive; unable to detect LV-GCA; patients with MR-incompatible devices
CTA	+	GCA, 73%*; TA, 100%*	GCA, 78%*; TA, 100%*	Stenosis; aneurysm dilation; mural thickening±enhancement	±	Assess burden; detect complications	Radiation exposure; iodinated contrast load
MRA	+	GCA, ND; TA, 100%*	GCA, ND; TA, 100%*	Stenosis; aneurysmal dilation; mural thickening±enhancement	±	Assess burden; detect complications; no radiation exposure; integrated cardiac images	Less accessible; expensive
PET	+	GCA, 76%–90%; TA, 70%–87%	GCA, 89%–98%; TA, 73%–84%	Increased mural tracer uptake	±	Assess burden and activity; combined with CT/MR for hybrid structural and functional imaging	Radiation exposure; current tracers lack specificity

Sensitivity and specificity values are pooled from available studies reviewed in references.[43,44] CT indicates computed tomography; CTA, computed tomography angiography; GCA, giant cell arteritis; LV-GCA, large vessel giant cell arteritis; MR, magnetic resonance; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; ND, no data; PET, positron emission tomography; TA, Takayasu arteritis; and US, ultrasound.

*Data derived from a single study.

technique for diagnosis and is recommended as the primary imaging modality of choice by European League Against Rheumatism.[43] Detection of homogenous hypoechoic mural thickening, the halo sign, has a reported pooled sensitivity and specificity of 77% and 96%, respectively, which rises to 100% specificity if present bilaterally or persists despite luminal compression.[43] However, a recent multicenter study of 381 patients with suspected GCA reported a much lower sensitivity of 54% with ultrasound, but this still compared favorably to that of temporal artery biopsy (39%).[45] The use of sonographers with less experience may have contributed to the observed lower sensitivity of ultrasound and highlights its operator-dependent limitations. Although ultrasound cannot reliably assess aortic involvement in LVV, it can identify axillary and femoral vasculitis.[46,47] Assessment of the axillary arteries is particularly useful for diagnosis as they are not commonly affected by atherosclerosis compared with lower limb vessels, which can affect the utility of femoral vessel assessment.[48] The role of ultrasound in disease monitoring is unclear as time to regression of the halo sign after starting treatment is highly variable and halo signs around larger vessels may persist for months to years.[48]

CT Angiography

CTA provides a structural assessment of extracranial and aortic vessels. It can report the extent of LVV and delineate mural thickening, luminal stenosis (Figure 2), and aneurysmal dilation, as well as mural contrast enhancement (assumed to represent active vasculitis).[44] Thus, CTA may be able to monitor development of vascular complications in patients with LVV, such as aortic aneurysms. Prospective data supporting the role of CTA for diagnosis of LVV are few but show evidence of large vessel involvement in ≈70% of patients with biopsy-proven, active GCA.[49,50] Data on tracking disease activity with CTA are equally scarce but have reported persistent mural thickening on follow-up imaging in two-thirds of patients with biopsy-proven GCA despite clinical and biochemical remission.[51] However, nearly all patients had resolution of mural contrast enhancement on repeat CTA,[51] suggesting that current CTA-derived metrics may be too coarse to reliably track disease. The high effective radiation dose of CTA limits its use in young patients and for serial imaging, but evidence supporting the safety of low-dose CT protocols may change this.[52] This is important in practical terms as CT is more widely accessible than magnetic resonance (MR). Regardless, the use of iodinated contrast carries the risks of allergic reactions as well as contrast-related kidney dysfunction.

MR With or Without Angiography

MR with or without angiography provides superior soft tissue contrast compared with CTA, avoids exposure to ionizing radiation (Figure 3), and is the recommended modality for diagnosis of suspected TA given the younger age of affected patients.[43] High-resolution MR of cranial vessels has a similar sensitivity and specificity to ultrasound for the diagnosis of cranial GCA and thus is recommended if ultrasound is inconclusive or unavailable.[43] After contrast administration, mural enhancement on T1-weighted images is suggestive of active vessel inflammation. Suppression of signals from both adipose tissue (by fat saturation or short T1 inversion recovery sequences) and blood flow (black-blood sequences) enhances visualization of mural contrast uptake particularly in the carotid, subclavian, and axillary arteries, which lie close to subcutaneous and fascial fat. T2-weighted images can demonstrate mural edema indicative of vasculitis but are considered by European League Against Rheumatism to be less sensitive

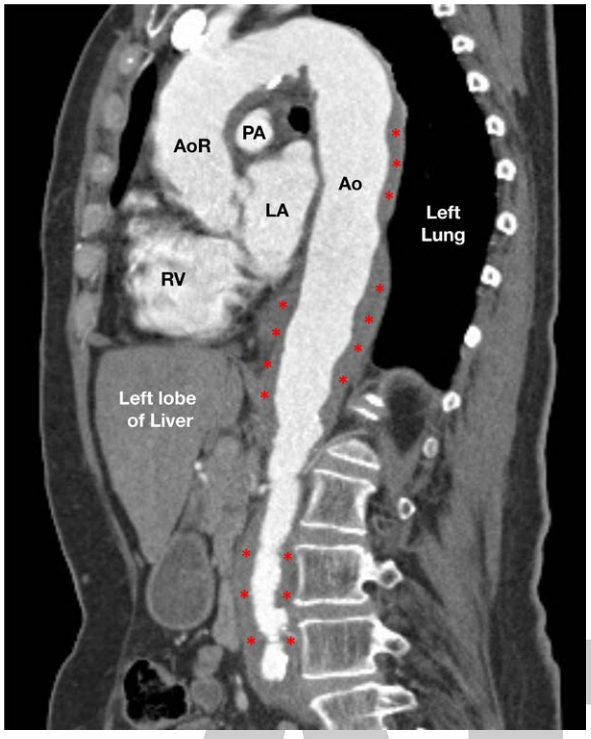

Figure 2. Computed tomography (CT) angiography in large vessel vasculitis (LVV). Coronal oblique multiplanar reconstruction contrast-enhanced CT with angiography demonstrating diffuse mural thickening of the thoracic and abdominal aorta (Ao; red asterisks) in a patient with LVV. AoR indicates aortic root; LA, left atrium; PA, pulmonary artery; and RV, right ventricle.

and prone to artifact.[43] MRA can also assess the wider vasculature to define disease extent and is, therefore, attractive for the longitudinal monitoring of vessel structure. A recent study of both patients with GCA and TA at various stages of their disease found that MRA provided better evaluation of disease extent compared with PET but correlated poorly with clinical and circulating measures of disease activity.[53] Glucocorticoids and biologic therapy can modify mural edema and enhancement on MRA,[54] but the heterogenous nature of the study population in terms of age, disease type, and duration may explain the observed discordance between imaging and clinical assessment.[53] A further strength of MR imaging is that specific cardiac sequences can be readily integrated alongside vascular imaging, which is particularly relevant for TA. This approach has been shown to be feasible[55] and can provide assessments of left ventricular volume, ejection fraction, aortic root dilation, and myocardial scarring alongside standard assessments of vasculitis disease activity and burden.[55] Such data may identify patients at high risk of poor outcomes who might benefit from targeted intervention, but this requires evaluation in large studies. Limitations of MR include its availability, cost, and patient tolerability, particularly if multiple vessel beds are imaged. Lack of availability may limit its use in GCA where rapid diagnosis and therapy are essential to avoid irreversible visual loss.

An important limitation of both CTA and MRA is a lack of standardized imaging-based outcome measures for disease burden and activity. Both European League Against Rheumatism and the Outcome Measures Rheumatology groups have highlighted the urgent need for such measures for use in clinical trials.[43,57] A recent study designed a cross-platform angiographic scoring system applicable to both CTA and MRA images.[58] This was then validated in a cross-sectional and longitudinal study of 131 patients (96 with TA, 35 with GCA), and scoring correlated well with disease burden at baseline, subsequent disease activity, and progression of vascular lesions.[58] External validation in larger prospective studies is required to examine the utility of this system further.

Molecular Imaging

Positron Emission Tomography

Both CTA and MRA provide detailed structural assessments of vessel inflammation, but treatment decisions are primarily influenced by disease activity—a functional metric. PET is a highly sensitive molecular imaging technique that employs radiotracers to measure the activity of metabolic

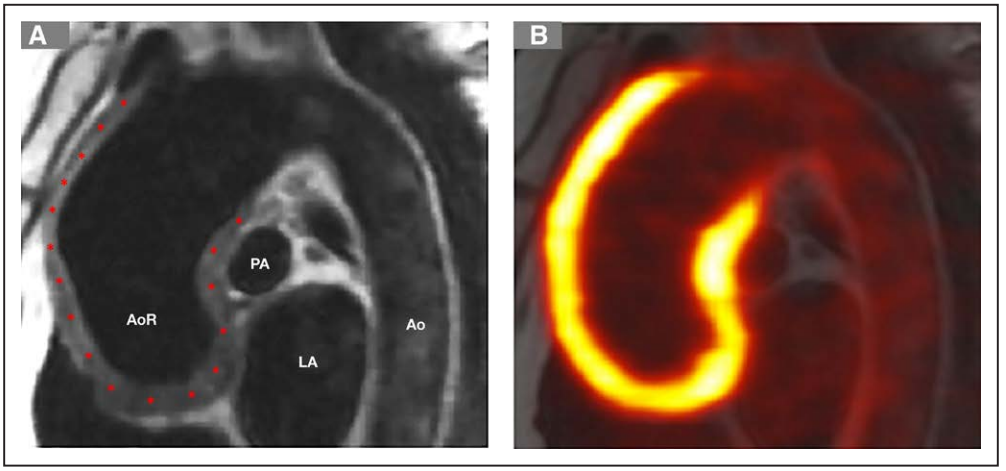

Figure 3. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)–magnetic resonance (MR) in large vessel vasculitis. **A**, Cardiac MR image with black-blood sequence in the sagittal plane demonstrating circumferential mural thickening of AoR (aortic root) and ascending Ao (aorta; red asterisks). **B**, Same MR sequence fused with ^{18}F-FDG PET showing diffuse homogenous FDG uptake along the length of ascending Ao in keeping with severe active vasculitis. LA indicates left atrium; and PA, pulmonary artery. Adapted from Tarkin et al[56] with permission. Copyright © 2016, the Authors.

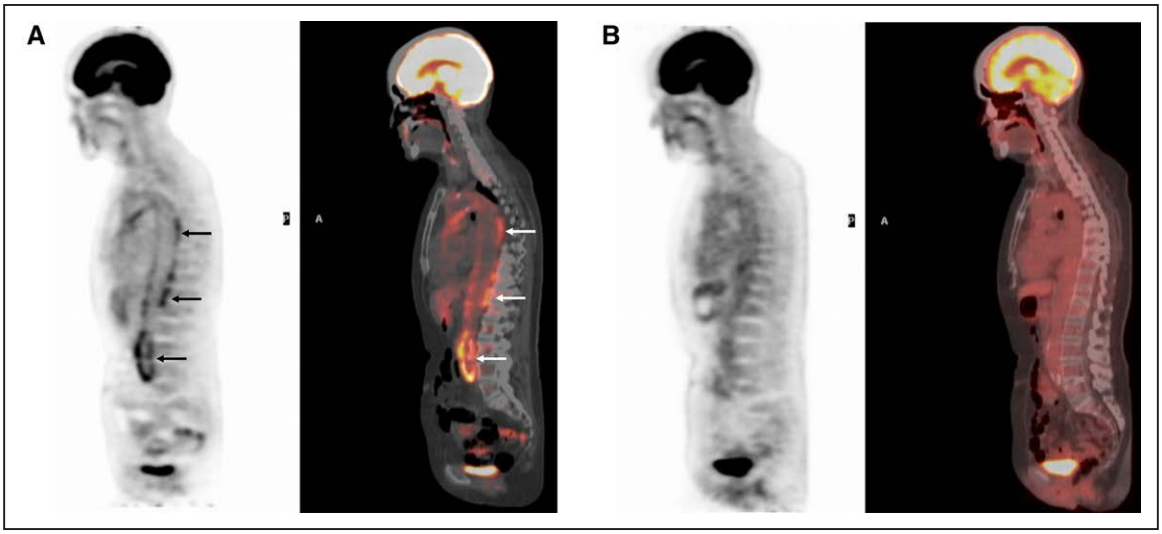

Figure 4. Assessing disease activity in large vessel vasculitis (LVV) with positron emission tomography (PET). **A**, Sagittal attenuated corrected ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET (**left**) and fused ^{18}F-FDG PET-computed tomography (CT; **right**) images from a patient with active LVV before treatment. Images show diffuse increased FDG uptake in relation to the aortic wall (black and white arrows) corresponding to the mural thickening demonstrated on the CT in Figure 3. **B**, Repeat ^{18}F-FDG PET-CT images obtained after 6 mo of treatment with glucocorticoids and successful clinical remission demonstrates resolution of the abnormal mural aortic FDG uptake.

processes in vivo. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is a glucose analogue that contains an 18-fluoride group in place of a hydroxyl group. After uptake into cells by GLUT (glucose transporter) proteins, ^{18}F-FDG undergoes phosphorylation by hexokinase; however, the 18-fluoride group prevents entry into downstream metabolic pathways. Reconversion of phosphorylated ^{18}F-FDG by glucose-6-phosphatase is slow, and the end product is unable to exit the cell because of its negative charge.[59] Consequently, ^{18}F-FDG is trapped intracellularly undergoing emission decay that is detected by scintigraphy. Thus, ^{18}F-FDG reports cellular glucose utilization as a marker of cellular metabolic activity.[59]

Cells with high glycolytic activity show greater ^{18}F-FDG uptake because of greater GLUT expression.[59] Macrophages, monocytes, and lymphocytes have all been shown to upregulate GLUT-1, GLUT-3, and GLUT-5 expression in response to inflammatory stimuli, represented by avid ^{18}F-FDG uptake in inflamed tissues.[60–62] ^{18}F-FDG PET has been widely used to study atherosclerotic inflammation where the intensity of tracer uptake reflects plaque macrophage burden.[63] These properties provide a biological rationale for ^{18}F-FDG PET imaging in vasculitis.[63] PET involves around 50% of the effective radiation of a diagnostic CT but is often combined with low-dose attenuation correction CT or MR to provide precise anatomic localization of tracer uptake (Figure 4).[43]

PET in LVV

^{18}F-FDG is the most widely studied PET radiotracer with prospective data supporting its utility in the diagnosis of LVV.[64–69] A recent meta-analysis of predominantly prospective studies totaling 170 patients reported a pooled sensitivity of 76% and specificity of 93% of ^{18}F-FDG PET for diagnosing LVV.[70]

There are few data with respect to tracking disease activity longitudinally. Blockmans et al[71] studied 35 patients with GCA who had a temporal artery biopsy followed by a baseline ^{18}F-FDG PET before treatment and then the scan was repeated at 3 and 6 months. ^{18}F-FDG uptake fell significantly at 3 months compared with baseline, but ongoing vessel uptake persisted in >50% of patients at 6 months despite clinical and biochemical remission.[71] Grayson et al[72] recruited 56 patients with LVV (30 GCA, 26 TA) and 59 comparator subjects (35 with hyperlipidemia, thus more likely to have aortic atherosclerosis; 17 LVV mimics and 9 healthy controls). Thirty-five patients with LVV had a follow-up PET scan with a mean interval of ≈6 months. Qualitative ^{18}F-FDG uptake was significantly greater in patients with LVV compared with comparator subjects and in active disease compared with remission. In addition, greater global ^{18}F-FDG uptake while in clinical remission was predictive of future relapse.[72] Importantly, 17% of patients in the comparator group had ^{18}F-FDG uptake qualitatively interpreted as active vasculitis, highlighting the limitations of this tracer as specific marker of disease activity in LVV. Similar limitations have been encountered in TA where patients with prosthetic vascular grafts demonstrated increased ^{18}F-FDG uptake in grafts on PET-CT despite clinical or biochemical remission and no evidence of graft infection.[73] Follow-up PET imaging (n=9) ≈15 months later showed no change in graft ^{18}F-FDG uptake despite the use of additional immunosuppression in the intervening period.[73]

The available data show discordance between imaging-reported vessel inflammation and clinical markers of disease activity. Whether persisting ^{18}F-FDG uptake or mural thickness represents subclinical vasculitis, remodeling, or atherosclerosis is unclear and is a critical area for further study. Addressing this issue will require hybrid imaging modalities, better delineation of mural tracer uptake patterns, greater metabolic specificity of tracers, and clearly defined clinical end points. The advent of hybrid PET-MR for LVV[29] with its superior soft tissue contrast and lower radiation exposure for serial imaging may be the likeliest platform to help achieve this, but the limited available data are conflicting.[29,74] The diagnostic sensitivity of ^{18}F-FDG PET for active GCA appears preserved

for ≤3 days after commencing glucocorticoids[65] but falls significantly by 10 days,[75] highlighting the particular challenge of accessibility to novel imaging modalities when prompt treatment is essential.

Medium Vessel Vasculitis

Clinical Context and Challenges

Polyarteritis nodosa (PAN) is the predominant MVV in adults. Kawasaki disease—the other major form of MVV and an acute arteritis of childhood—is discussed elsewhere.[76] PAN is uncommon with an estimated incidence of 1 to 10 per million.[77] Both sexes are affected equally, and the peak age range of onset is between 40 and 60 years.[78] The etiopathogenesis of PAN is strongly linked to viral hepatitis infection, particularly hepatitis B virus,[79] which compromised over one-third of 348 PAN cases in the largest case series to date.[78] The incidence of hepatitis B virus–related PAN has declined substantially over the last 4 decades after improvements in immunization, transfusion practice, and hepatitis B virus therapy.[78,80]

PAN can manifest as a systemic vasculitis or a skin-limited form, cutaneous PAN. Both are characterized by a transmural necrotizing arteritis of muscular arteries. The most commonly affected sites are the skin (causing livedo reticularis and ulceration) and peripheral nerves (leading to a mononeuritis multiplex).[4] Involvement of visceral vessels is also common with multiple irregular arterial stenoses and microaneurysms demonstrable (Figure 5) on contrast angiography in ≤90% of patients[81,82] These can occur in any organ but are the most frequent in the renal and mesenteric arteries; however, reliable frequency data are limited by sampling bias.[78] Renal involvement can lead to segmental renal infarction and impaired renal function, as well as hypertension, whereas mesenteric disease manifests as gut ischemia, perforation, and hemorrhage from aneurysm rupture.[78] Despite treatment, mortality may be as high as 35% at 5 years in those with severe disease as indicated by the Factor Five Score.[78,83]

Novel Mechanisms and Potential Treatments

Pathogenesis of PAN

Compared with other vasculitides, the pathogenesis of PAN is poorly understood. Endothelial injury, through immune complex deposition and viral replication, has been proposed as a key trigger in hepatitis B virus–related PAN.[84] This is supported by the success of antiviral therapy and plasma exchange in achieving sustained remission but does not explain the residual majority of PAN, which is noninfection related. In these cases, long-term immunosuppression with glucocorticoids alongside other agents such as cyclophosphamide, methotrexate, or azathioprine improves patient outcomes and supports an autoimmune component to pathogenesis.[85] However, relapse rates can reach 50% at 2 years, and these drugs have significant side effects.[78]

T-Cell Activation and ADA2 in PAN

Recent studies exploring immunopathogenesis have found higher IFN-γ expression in $CD4^+$ T cells in patients with PAN compared with patients with granulomatosis with polyangiitis (GPA) but noticeably lower IL-17 expression.[86] IFN-γ is a potent inhibitor of regulatory T-cell function, and this same study found significant impairment in the immunosuppressive potential of regulatory T cells isolated from patients with PAN compared with those isolated from healthy controls.[86] The relative lack of IL-17 expression seen in this study may partly explain the absence of granulomata in PAN, compared with LVV where IL-17 (from Th17 cells) and IFN-γ (from Th1 cells) synergistically lead to granuloma formation.[22] Blocking T-cell activation in PAN using TNFα (tumor necrosis factor-α) blockers or TCZ has shown some promise in limited case series.[87–89]

The identification of a potential genetic basis for PAN has provided novel perspective into pathogenesis and renewed interest in the potential role of TNFα blockade. Whole-exosome and candidate gene sequencing of patients with familial PAN and PAN-like syndromes and unaffected family members has identified several novel loss-of-function homozygous or compound heterozygous mutations of genes encoding ADA2 (adenosine deaminase 2), formerly known as cat eye syndrome *CECR1* gene.[90,91] The predominant site of ADA2 expression is in myeloid cells, which export ADA2 into the extracellular compartment.[92] In vitro data have shown that ADA2 drives monocyte differentiation and proliferation of macrophages and $CD4^+$ T cells[92] and that ADA2 knockout skews monocyte polarization toward an inflammatory M1 phenotype with subsequent disruption of endothelial layer integrity.[90] Thus, deficiency of ADA2 may initiate a vicious cycle of inflammation and vascular disruption that manifests as a systemic medium vasculopathy with the clinical and histopathologic features of PAN. Indeed, many patients with deficiency of ADA2 syndromes fit the diagnostic criteria for PAN.

The vasculopathy associated with loss of ADA2 typically presents in childhood, but adult presentations have also been reported.[90,91,93,94] Across various series, these patients show variable responses to standard treatments for PAN. In the largest European study, glucocorticoids while initially effective were associated with relapse on tapering.[94] Other treatments such as cyclophosphamide, methotrexate, and azathioprine were ineffective at controlling disease during steroid taper.[94] However, in both European[94] and ultrasound[91] series, TNFα blockade has shown consistent efficacy in suppressing vasculitis, although what constitutes response was not clearly or uniformly defined. This efficacy extended to patients with life-threatening disease despite maximal tolerated doses of cyclophosphamide.[91]

Why TNFα blockade is particularly effective in deficiency of ADA2 vasculopathy is unclear. Skin biopsies from these patients show a necrotizing, nongranulomatous MVV with abundant staining for TNFα,[90] but further work is needed to clarify the precise mechanisms. The relevance of ADA2 to all forms of PAN is also unclear. ADA2 activity appears important in the immune response to infections, particularly intracellular pathogens.[95] It is possible that more subtle impairments of ADA2 could be induced or exacerbated by intracellular infection thereby promoting immune dysregulation and vascular injury. Assessing *ADA2* gene expression in all patients presenting with PAN is potentially feasible

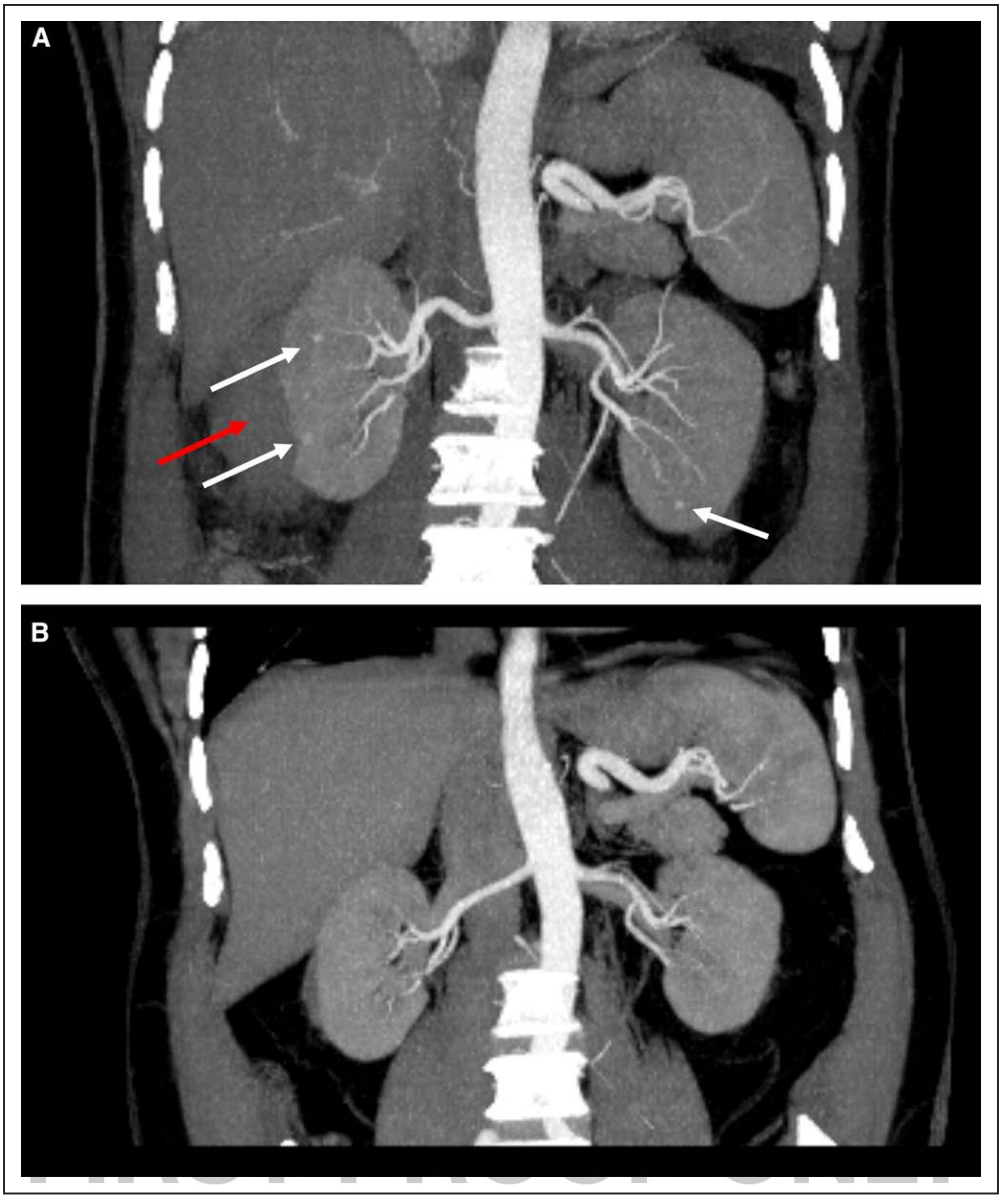

Figure 5. Computed tomography angiography (CTA) in polyarteritis nodosa. **A**, Coronal maximum intensity projection CTA demonstrating bilateral intrarenal microaneurysms (white arrows) and a large right subcapsular perinephric hematoma (red arrow). **B**, Repeat CTA 6 mo later following immunosuppressive treatment and achievement of clinical remission shows resolution of radiological changes.

given its low incidence and may reveal a novel pathway of pathogenesis.

Imaging in PAN

Structural and Molecular Imaging

Microaneurysms or arterial stenoses are present in a majority of patients with PAN at presentation.[78,81,82] Fluoroscopic-guided contrast angiography is considered the optimal modality for identifying these abnormalities with a reported sensitivity and specificity of ≈90%.[96] However, this carries the risks associated with arterial cannulation including bleeding, embolization, and pseudoaneurysm formation in addition to risks of contrast administration such as allergic reactions and renal dysfunction. CTA and MRA provide a noninvasive assessment of but may be less sensitive for the detection of microaneurysms (typically 1 to 5 mm in size).[97] Although ^{18}F-FDG PET has been used in small studies of PAN, showing increased uptake in medium arteries,[98] its use has not been adequately assessed.

Similar to LVV, assessment of disease activity is challenging in PAN. The vast majority of imaging data in PAN relate to diagnosis with fluoroscopic contrast angiography. Data for CTA and MRA are limited to individual case reports and case series with CTA and MRA. However, interval imaging across all 3 modalities shows resolution of microaneurysms with disease remission[99,100] (Figure 5) and progression of lesions with refractory disease,[101] thus may provide useful additional information on top of standard clinical and biochemical parameters. The lack of ionizing radiation makes MRA an attractive modality for future longitudinal studies to track disease activity. Hybrid PET/MR imaging may enable more refined tracking

Table 2. Clinical and Biochemical Features of ANCA-Associated Vasculitis Subtypes[8,107,108]

Features	GPA	MPA	EGPA
Incidence, per million per y	5–10	6–8	1–3
ANCA present, %	≈50%–90%	≈90%	≈40%
Predominant subtype	PR3	MPO	MPO
ENT involvement	+++	+	++
Lung involvement	++	++	+++
Pulmonary hemorrhage	+	++	–
Kidney involvement	++	+++	+
Nerve involvement	+	++	+++
Unique features	Orbital disease; airway stenosis	Interstitial lung changes	Eosinophilia; cardiac disease; adult-onset asthma

ANCA indicates antibody to neutrophil cytoplasmic antigens; EGPA, eosinophilic granulomatosis with polyangiitis; ENT, ear, nose, and throat; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; and PR3, proteinase-3.

of disease activity particularly in patients with visceral vessel lesions that are at high risk of catastrophic complications.

Small Vessel Vasculitis

Clinical Context and Challenges

ANCA-associated vasculitis is the commonest systemic SVV in adults and has an incidence of 20 to 30 per million population.[102] It is characterized by necrotizing inflammation of small arteries, arterioles, and capillaries, usually in the presence of autoantibodies directed against the neutrophil cytoplasmic granular proteins PR3 (proteinase-3) and MPO (myeloperoxidase),[1] although ≈10% patients with the characteristic clinical and histological features of ANCA-associated vasculitis lack measurable circulating ANCA.[103] The peak age of onset of ANCA-associated vasculitis is in the fifth and sixth decade with no clear sex predominance.[102] There are 3 clinical subtypes, GPA, microscopic polyangiitis, and eosinophilic GPA (EGPA); the key features of these are described in Table 2. From a clinical perspective, it is noteworthy that significant overlap between clinical subtypes exists.[1] More recently, focus has shifted to classification by ANCA subtype after the discovery of genetically distinct origins for MPO and PR3 ANCA.[104] These differences may underpin the recognized differences in clinical expression of disease[105] and have future implications for treatment. Overall, however, the risk of premature mortality is >2.5× greater than in an age- and sex-matched general population.[106]

Fifty percent of patients with ANCA-associated vasculitis experience a relapse within 5 years of diagnosis.[109] PR3+ disease is frequently associated with granulomatous inflammation, as well as higher rates of relapse and refractory disease.[105] The reasons for this are unknown but may relate to their differing genetic basis of ANCA subtypes.[104] In addition, granulomata may act as tertiary lymphoid organs[110] and harbor autoreactive B cells facilitating their escape from autodeletion or depletion by cytotoxic treatments. As with LVV, persisting low-grade inflammation contributes to the development of cardiovascular disease morbidity and mortality.[7] Treatment of ANCA-associated vasculitis is divided into distinct induction and maintenance phases.[111] The goal of induction therapy is rapid, effective suppression of the immune response to limit inflammatory organ injury. Maintenance therapy provides lower intensity immunosuppression over the medium to long term to prevent disease relapse and accrual of organ damage. In both phases, achieving effective immunosuppression while minimizing toxic side effects is challenging.[112] Agents such as cyclophosphamide and rituximab are effective but similarly associated with an increased risk of infection and cancer.[112] Finally, the lack of reliable tools for assessing disease activity while on treatment and stratifying the risk of future relapse are critical challenges. This makes it difficult not only to identify patients with ongoing disease activity who require treatment escalation but also patients who are at low risk of relapse who can safely stop potentially toxic immunosuppression.

Novel Mechanisms and Treatments

B Cells in ANCA-Associated Vasculitis

The introduction of the alkylating agent cyclophosphamide 4 decades ago transformed the short-term prognosis of ANCA-associated vasculitis.[113,114] Cyclophosphamide efficacy is attributable to depletion of all major leucocyte subsets,[115] but a marked suppressive effect on circulating lymphocytes, particularly B cells, was noted in several early studies.[115–117] Subsequent histological evidence of activated B cells in granulomata from patients with GPA,[118] the role of B cells in antibody-mediated autoimmunity, and strong evidence for the pathogenicity of ANCA,[104,119] all support an important role for B cells in the pathogenesis of ANCA-associated vasculitis and provide a rationale for targeted B-cell depletion (Figure 6). Furthermore, the side effects of cyclophosphamide, including an increased risk of malignancy, infection, and infertility,[112] are a leading factor in the search for selective B-cell targeting.

B-Cell Depletion

The chimeric monoclonal antibody rituximab selectively depletes CD20 expressing B cells, and its development represents the most important therapeutic advance in ANCA-associated vasculitis since cyclophosphamide. The RAVE[120] and RITUXVAS[121] trials established noninferiority of rituximab to cyclophosphamide for remission induction of ANCA-associated vasculitis including for those with organ and life-threatening presentations. At 18 to 24 months of follow-up, rituximab induction with no additional maintenance therapy continued to demonstrate noninferiority to cyclophosphamide induction with azathioprine maintenance in relation to rate of relapse, end-stage renal disease, and death.[122,123] Importantly, the cumulative dose of glucocorticoids was no different between the 2 groups.[122,123]

Sustained B-cell depletion with a suppressed ANCA was associated with the lowest risk of relapse in RAVE and RITUXVAS.[122,123] However, B-cell return occurred as early as 6 months after rituximab, and most patients had B-cell repopulation by 18 months post-dose.[43] The MAINRITSAN trial explored whether, after cyclophosphamide induction,

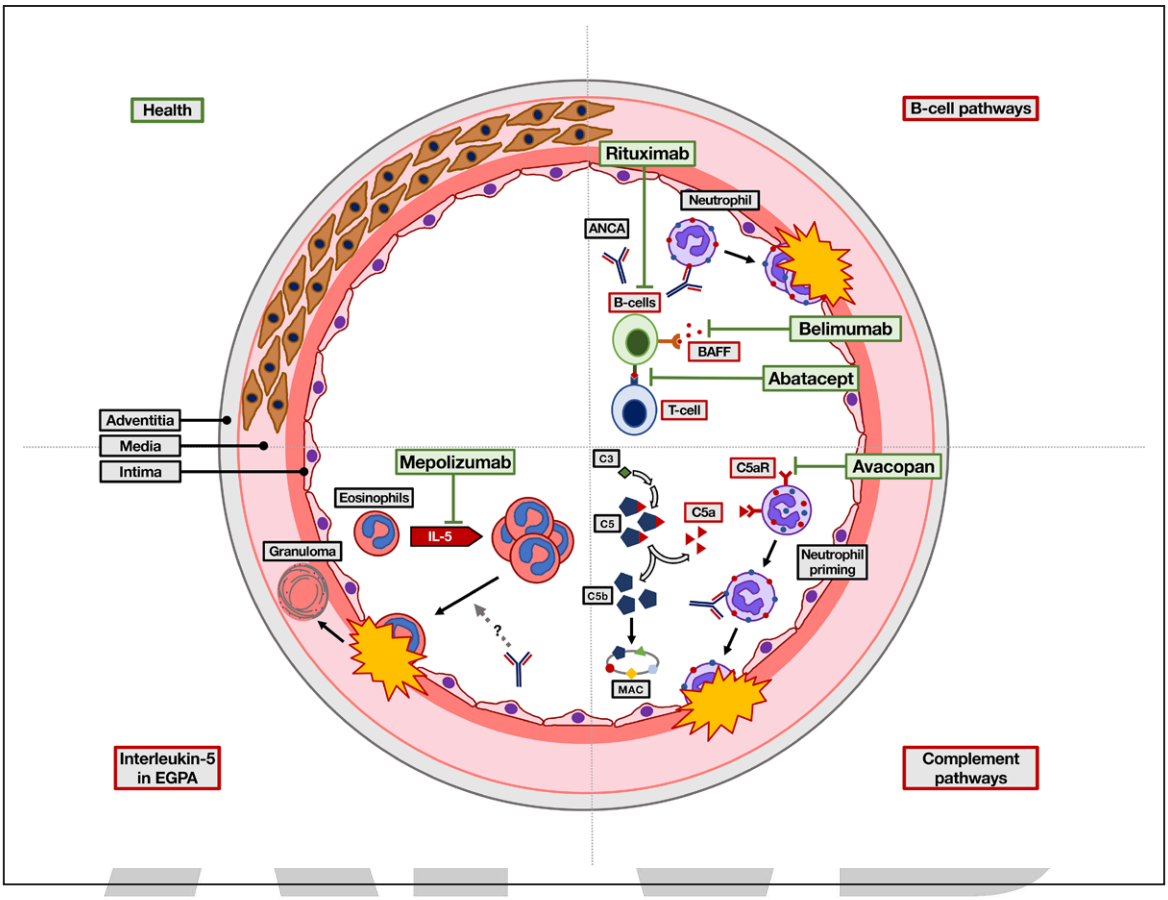

Figure 6. Targeting key mechanisms in the pathogenesis of antibody to neutrophil cytoplasmic antigens (ANCA) vasculitis. Cross-sectional diagram of a small artery depicting important pathogenic pathways of ANCA vasculitis. **Upper left** shows vessel structure in health; **upper right** shows the B-cell pathways; **lower right** shows the alternative complement pathway; **lower left** shows IL (interleukin)-5 in eosinophilic granulomatosis with polyangiitis (EGPA). B-cell involvement in antibody production, T-cell costimulation, and B-cell activation contribute to production and binding of circulating ANCA to primed neutrophils expressing cytoplasmic antigens PR3 (proteinase-3; red circles) and MPO (myeloperoxidase; blue circles). ANCA binding triggers neutrophil degranulation with subsequent endothelial injury. Depleting B cells by with rituximab, blocking costimulation with abatacept and inhibiting B-cell activation factors like BAFF (B-cell activating factor) with belimumab offers sophisticated inhibition of these pathways. Binding of complement protein C5a to its surface receptor on neutrophils leads to translocation of PR3 and MPO to the surface (neutrophil priming). Subsequent binding of circulating ANCA results in endothelial injury. Avacopan inhibits C5a binding. IL-5 promotes proliferation and migration of eosinophils out of bone marrow into the circulation. The precise steps that trigger subsequent eosinophil-mediated vascular injury are unclear but may involve ANCA. Targeting of IL-5 in EGPA is now possible using the monoclonal antibody mepolizumab. C5aR indicates C5a receptor; and MAC, membrane attack complex.

rituximab administered every 6 months for 18 months would offer greater protection against relapse versus standard-of-care azathioprine. Major relapse rates were significantly lower in the rituximab group (5% versus 29%; P=0.002).[124] The benefits of rituximab extended for ≤5 years after enrollment and were associated with a modest improvement in survival.[125] However, tailoring maintenance treatment with rituximab according to the B-cell count or ANCA titer does not appear to be any better (or worse) than fixed-interval dosing in terms of efficacy and safety.[126]

What Next for B-Cell Depleting Therapy?

The optimal dosing interval for rituximab remains unclear. The RITAZAREM trial is in progress and explores whether higher dose rituximab (1000 mg) given more frequently (every 4 months for 5 doses) after rituximab induction for relapsing ANCA-associated vasculitis will provide greater protection compared with azathioprine.[127] RAVE and RITUXVAS did not include patients with EGPA; so it is unclear whether the benefits of B-cell depletion translate to this unique subtype of ANCA-associated vasculitis. However retrospective data suggest potential benefit of rituximab particularly in EGPA associated with circulating ANCA.[128] The ongoing REOVAS[129] and MAINRITSEG[130] trials will shed light on the utility of this approach for induction and maintenance therapy in EGPA, respectively.

Although recommended for remission induction and maintenance therapy in ANCA-associated vasculitis,[111] the available data do not support rituximab as being safer than other immunosuppressive agents. In clinical trials, the frequency of infections following rituximab was similar to cyclophosphamide, but this may be driven by concomitant glucocorticoid.[122,123] Reactivation of latent hepatitis B infection,[131] persisting hypogammaglobulinemia,[132] and late-onset neutropenia[133] are important side effects encountered with rituximab that contribute to morbidity. Furthermore, the chimeric structure of rituximab is immunogenic and has been linked to the development of infusion reactions and antichimeric antibodies that can limit its efficacy.[134] The development

of fully humanized anti-CD20 antibodies such as ofatumumab and obinutuzumab will hopefully address these issues.

However, the absence of consistent evidence showing an increased risk of cancer following B-cell depletion is a potential benefit of this treatment option.[135] Recent data from a single tertiary center reported a 3- and 4-fold increased risk of cancer (mainly nonmelanomatous skin cancer) with cyclophosphamide compared with the general population and patients receiving rituximab, respectively.[136] Interestingly, the apparent protective effects of rituximab against risk of malignancy showed a dose-dependent relationship[136]—a concept supported by experimental data.[137]

B-Cell and T-Cell Costimulation and Depletion

The presence of granulomatous T-cell infiltrates in lung[138] and renal biopsies[139] along with impaired regulatory T-cell function in blood samples from patients with ANCA-associated vasculitis glomerulonephritis suggests a pathogenic role of T cells (Figure 6).[140] Recent attention has focused on blocking T-cell costimulation by activated, antigen-presenting B cells with abatacept. In an open-label trial of 20 patients with a nonorgan threatening relapse of GPA, abatacept led to disease remission in 80% and steroid discontinuation in ≈75% with a safety profile comparable to other treatment options.[141] An option for managing nonsevere relapse that permits steroid minimization would be of major clinical value in ANCA-associated vasculitis. The ongoing multicenter, randomized placebo-controlled ABROGATE trial should define to what extent abatacept can achieve this.[142]

Depletion of both B and T cells can be achieved using alemtuzumab—a monoclonal antibody with specificity for CD52. CD52 is also expressed, in lower abundance, on monocytes/macrophages and eosinophils[143]; thus alemtuzumab exerts effects on a range of cellular components involved in the pathogenesis of ANCA-associated vasculitis. Retrospective data suggest a role for alemtuzumab as induction therapy for severe/refractory ANCA-associated vasculitis but also reported high rates of infection and malignancy following its use.[144] An open-label phase IV trial is in progress.[145]

B-Cell Survival and Relapse: Targeting BAFF

B-cell maturation is influenced by several cytokines including BAFF (B-cell activating factor; also known as BlyS [B-lymphocyte stimulator]) and is increasingly recognized as important in the pathogenesis of relapsing ANCA-associated vasculitis. BAFF signaling regulates the transition of naive B cells into memory B cells and mature plasma cells.[146] Increased BAFF expression is evident in patients with active vasculitis,[147] and preclinical data suggest that high BAFF concentrations can promote the survival of autoreactive B cells that under normal conditions would be deleted.[148] These autoreactive B cells can escape to peripheral lymphoid follicles where they may be less effectively depleted by anti-CD20 therapies.[110] In addition, B-cell depletion appears to increase concentrations of BAFF.[149] Thus, B-cell depleting therapies in the context of high levels of BAFF may promote survival of autoreactive B cells that are able to trigger relapse during B-cell repopulation.

Belimumab is a fully humanized monoclonal antibody that prevents circulating BAFF binding to BAFF receptors on B cells (Figure 6). In trials of patients with systemic lupus erythematosus, this approach was effective in reducing relapse and glucocorticoid requirements.[150] In ANCA-associated vasculitis, the BREVAS study attempted to compare belimumab to azathioprine for maintenance of remission in GPA and microscopic polyangiitis. However, the trial was stopped early because of suboptimal recruitment with no concrete evidence of improved benefit. Combining BAFF targeting with other anti–B-cell therapies may offer additional benefit by preventing autoreactive B-cell escape and enabling more complete B-cell depletion.

Alternative Complement Pathway: Targeting C5a Receptors

The complement system is a central mediator of antibody-mediated immune responses.[151] C5 is a potent effector protein in this pathway, exerting its effects through its cleavage products C5a, a powerful chemoattractant, and C5b, part of the membrane attack complex that lyses target cells.[152] Activation of the alternative complement pathway is evident in ANCA-associated vasculitis. Kidney biopsies from patients with ANCA-associated glomerulonephritis show deposition of alternative pathway components in active glomerular lesions.[153] In addition, high circulating levels of C3, C5a, and soluble C5b-9 (membrane attack complex) have been found in patients with active vasculitis, which subsequently fall in disease remission.[154] In vitro, C5a primes neutrophils for ANCA-induced degranulation that leads to endothelial injury (Figure 6).[155] Finally, in murine MPO models, knocking out C5a and C5aR (C5a receptor) is protective against the development of necrotizing glomerulonephritis, as is pharmacological blockade of C5aR.[156,157]

Clinical trial evidence of the utility of the C5a receptor inhibition with avacopan has recently emerged.[158] Sixty-seven patients with ANCA-associated vasculitis were randomized to either high-dose glucocorticoids, avacopan plus low-dose glucocorticoids, or avacopan alone alongside cyclophosphamide or rituximab induction. The primary end point of treatment response at 12 weeks (a 50% reduction from baseline in the Birmingham Vasculitis Activity Score) occurred in 86% of the avacopan/glucocorticoid and 81% of the avacopan-alone groups, compared with 70% in the glucocorticoid group (P=0.002 and P=0.01, respectively). Markers of renal injury and inflammation fell across all groups, but reductions occurred earlier and were of a greater magnitude with avacopan. Serious adverse effects such as psychiatric disturbances and new-onset diabetes mellitus were more common in the high-dose glucocorticoid group.[158] These promising results suggest that glucocorticoid-free remission induction in ANCA-associated vasculitis is achievable with novel targeted therapies. The ongoing larger and of longer duration phase 3 ADVOCATE trial will explore this further.[159]

Eosinophils in EGPA: Targeting IL-5

The immunopathology of EGPA is unique: it often lacks circulating ANCA, and the role of B cells and associated cytokines such as BAFF is unclear.[160] Indeed, ANCA-negative EGPA and ANCA-positive EGPA (predominantly because of circulating MPO ANCA) are increasingly recognized as

separate diseases with distinct genetic associations and clinical features.[161] ANCA-negative EGPA has associations with single-nucleotide polymorphisms within the IL-10 promoter gene,[162] whereas ANCA-positive forms are frequently associated with HLA-DRB1 and 7.[163] These genetics may explain, in part, the differences in clinical phenotype as cardiac involvement is much more common in ANCA-negative patients but renal and nerve involvement are more frequent in those with circulating ANCA.[164] In addition, a representative animal model does not exist, and patients with EGPA are underrepresented in the major clinical trials of ANCA vasculitis, thus they may not derive the same benefits from treatments with proven efficacy for other subtypes. A central feature of EGPA is a tissue and blood eosinophilia. IL-5 is a key mediator of this and stimulates eosinophil proliferation, survival, and migration into vessels and tissues (Figure 6).[160] Clinical studies have found high IL-5 concentrations in bronchoalveolar lavage samples of patients with active EGPA, which stimulates bronchospasm and bronchial eosinophilic infiltration.[165]

Mepolizumab is a fully humanized recombinant monoclonal antibody with specificity for IL-5. Small, open-label studies indicated the potential of mepolizumab to deplete circulating eosinophils, induce remission, and allow steroid taper in EGPA.[166,167] A recent randomized, double-blinded trial assigned 136 patients with refractory or relapsing EGPA to monthly mepolizumab or placebo.[168] After 52 weeks, patients in the mepolizumab arm spent significantly more time in remission, with 28% spending >24 weeks in remission compared with 3% in the placebo group.[168] Serious adverse events were more frequent in the placebo arm, and mepolizumab was well tolerated. The relapse rate was high: 47% and 82% in the mepolizumab and standard-of-care arms, respectively. This may reflect the inclusion of patients with long-standing disease and a high tissue eosinophil burden that is resistant to IL-5 blockade.[168] Long-term treatment with mepolizumab may be necessary as relapse occurred rapidly following discontinuation. However, mepolizumab is an important advance in EGPA and received Food and Drug Administration approval in late 2017.

Imaging in ANCA-Associated Vasculitis

Despite validated tools such as Birmingham Vasculitis Activity Score, assessing disease activity in patients on treatment remains challenging in ANCA-associated vasculitis. While interval biopsies to assess disease activity may be more feasible compared with GCA, this approach is impractical. Thus, a noninvasive means of detecting small vessel inflammation would be equally valuable in SVV.

PET in ANCA-Associated Vasculitis

PET may provide additional information about disease activity in patients with lung or sinonasal involvement, typically seen in GPA. Standard CT offers coarse structural metrics of disease activity such as a reduction in size of nodules, masses, or mucosal thickening but often these do not fully resolve.[169] In addition, patients with GPA often report symptoms suggestive of disease activity[170] but lack a robust clinical measure of this. There are no prospective studies of the use of ^{18}F-FDG PET to monitor disease activity in ANCA-associated vasculitis, but retrospective studies have reported increased ^{18}F-FDG uptake in clinically affected organs.[171] Persistent ^{18}F-FDG uptake on follow-up imaging was seen in patients with elevated disease activity scores suggesting PET could at least match current tools.[171] Prospective studies are needed to explore whether this imaging modality can identify currently unidentifiable and subclinical smoldering disease.

Future Directions

New Indications for Established Drugs

Targeting VSMCs: the Endothelin System in LVV

Suppressing remodeling due to vasculitis may targeting of pathways beyond leucocyte-IL signaling. ET-1 (endothelin-1) is the most potent endogenous vasoconstrictor in man and is largely produced by endothelial cells.[172] ET-1 exerts its effects through 2 receptors: the ET_A (endothelin-A) and the ET_B (endothelin-B) receptor.[172] Within the vasculature, ET_A receptors are located on VSMC, whereas ET_B receptors are expressed on both VSMC and endothelial cells.[173] ET_A receptor activation is generally associated with pathological effects such as vasoconstriction, inflammation, and atherosclerosis,[173] whereas ET_B receptors mediate vasodilation and clearance of ET-1, although VSMC ET_B receptors do promote vasoconstriction.[173] Temporal artery biopsies from patients with GCA have revealed increased ET-1 peptide, ET_A, and ET_B, expression in arteritic lesions.[174,175] Additionally, a study of inflamed vessel explants from patients with GCA showed that ET-1 stimulated VSMC migration in vitro (Figure 1).[175] Furthermore, this outgrowth was inhibited by pretreatment with an ET_B antagonist and to a lesser extent by an ET_A antagonist.[175]

Pure ET_B antagonism is unlikely to be translatable to clinical settings given the potential deleterious effects of unopposed systemic ET_A activation. Ambrisentan, bosentan, and macitentan are dual $ET_{A/B}$ antagonists that are currently approved for use in pulmonary arterial hypertension.[176] Pulmonary arterial hypertension is characterized by florid VSMC proliferation in pulmonary vessels driven by an activated ET system, which can be ameliorated by $ET_{A/B}$ antagonism.[177] A similar role of ET-1 in vascular remodeling in LVV suggests a potential novel therapeutic indication for this drug class that is already available in the clinic. There are no registered clinical trials of ET receptor antagonism in LVV. However, ET antagonism has emerged as an important potential therapeutic strategy in chronic kidney disease with a recent large clinical trial demonstrating both efficacy and safety in slowing the loss of kidney function.[178]

Structural Imaging

Interrogating the Retinal Microvasculature

The eye acts as a window to the systemic and regional microvasculature. Systemic diseases such as hypertension and diabetes mellitus have profound effects on retinal microvessels as demonstrated by structural and functional retinal imaging.[179,180] Retinal optical coherence tomography captures the chorioretinal microcirculation, in particular, the highly vascularized choroid, with near-histological resolution.[181] In systemic disease, optical coherence tomography has revealed

retinal vessel remodeling and chorioretinal thinning in hypertension, diabetes mellitus, and CKD.[182–184] Additionally, preclinical and clinical optical coherence tomography have linked retinal microvascular pathology to circulating and histological markers of injury within the kidney.[184] We have shown that the highly vascularized choroid thins with increasing levels of systemic inflammation[184] potentially indicative of microvascular injury. In addition, in patients with ANCA-associated glomerulonephritis, we found that the severity of choroidal thinning mirrored the degree of vascular inflammation as represented by the number of glomerular crescents and focal necrotizing lesions on renal histology.[184] Studies to explore whether metrics are modified by treatment will clarify these associations further. The strong association between GCA and ischemic ocular complications such as arteritic ischemic optic neuropathy and retinal ischemia from choroidal hypoperfusion suggests optical coherence tomography may offer a novel means of identifying patients at risk of impending ischemic ocular complications.[185]

Novel MR/MRA Techniques for LVV

Improving MR imaging specificity for disease activity assessment in LVV is an important area for further research. Diffusion weighted imaging sequences detect the restriction of intracellular proton movement, typically in the context of cytotoxic edema following acute ischemia. Diffusion weighted imaging sequences are well established in MR imaging of acute stroke and highly sensitive for the detection of early infarcts. A recent proof-of-concept study hypothesized that the intense cellular infiltrate of LVV may also restrict proton movement within the vessel wall and thus be detectable using diffusion weighted imaging.[186] In combination with ^{18}F-FDG PET, diffusion weighted imaging was able to differentiate between overtly active, smoldering, inactive GCA and health.[186] Mural contrast enhancement as shown by conventional gadolinium-based contrast agents is assumed to represent active vessel inflammation but can also be seen in inactive disease.[187] Newer contrast agents such as gadofosveset trisodium are better retained in the intravascular compartment and have shown promise in differentiating between active and inactive mural inflammation in a small study of TA.[188] Both these techniques require further study to better define their potential utility.

Molecular Imaging

^{18}F-FDG reliably reports vessel wall macrophage hypermetabolism, but this is prominent in atherosclerosis, as well as LVV, and discriminating between these pathologies is challenging.[189] The pattern of ^{18}F-FDG uptake in atheromatous disease is often focal and related to the intima unlike the linear, diffuse medial uptake in vasculitis.[190] Furthermore, in untreated LVV, ^{18}F-FDG uptake is intense (described as greater than liver uptake when using visual assessment scoring), whereas low-grade uptake (less than liver uptake) is suggestive of atherosclerosis.[190] Large arterial calcification identified by hybrid PET/CT may aid identification of atherosclerosis over LVV.[190] However, the lack of specificity of ^{18}F-FDG limits its use in assessing disease activity in patients on treatment where low-grade subclinical vasculitis and atheroma may coexist. The development of PET tracers to identify differential polarization of macrophages or immune checkpoint activity may offer a more precise means of assessing disease activity, as well as differentiating between vasculitic and atherosclerotic forms of vascular inflammation.

Imaging Macrophage Activation

Activated macrophages express a range of specific receptors that can be targeted by radiotracer ligands. TSPO (translocator protein; also known as peripheral benzodiazepine receptor) is expressed on mitochondria of phagocytic cells of mononuclear lineage. The ligand PK11195 has specificity for TSPO with binding confirming the presence of activated macrophages in atheromatous carotid endarterectomy specimens.[191] PET with 11C-PK11195 has been used widely in neuroinflammatory disease[192] because of increased TSPO expression in microglia, but data in LVV are limited. A small study suggested the potential for 11C-PK11195 to track disease activity in LVV, as well as differentiate between quiescent and unstable carotid atheroma, but no larger studies have followed.[193]

Gallium-68-labeled [1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid]-D-Phe1, Tyr3-octreotate (Ga-DOTATATE) is a PET tracer with specificity for the SST-2 (somatostatin receptor subtype 2) expressed by macrophages.[194,195] Recent data have demonstrated markedly increased SST-2 expression on activated macrophages with a proinflammatory M1 phenotype compared with both unstimulated and anti-inflammatory M2 macrophages.[196] In addition, Ga-DOTATATE uptake by carotid atheroma in endarterectomy specimens strongly correlated with macrophage burden and *SST-2* gene expression, while uptake on clinical PET-CT reliably identified culprit carotid and coronary lesions.[196] Moreover, Ga-DOTATATE was better than ^{18}F-FDG at identifying high-risk coronary plaques, and uptake was more discrete allowing precise anatomic description of uptake.[196] The power of Ga-DOTATATE to reflect macrophage behavior has exciting translational potential for LVV. Studies to assess SST-2 expression and Ga-DOTATATE uptake in temporal artery biopsy specimens with tracer uptake on concurrent PET imaging before and after immunosuppression are needed to fully evaluate its potential in LVV.

Imaging Immune Checkpoints

The PD-1 (programmed death-1)/PD-L1 (programmed death ligand-1) system is an immune checkpoint pathway involved in the regulation of T-cell responses to antigens.[197] Under normal conditions, interaction of PD-L1 with PD-1 leads to controlled suppression of exuberant T-cell activation by promoting T-cell apoptosis.[197] Overactivity of this checkpoint leads to impaired T-cell tumor surveillance, and therapeutic inhibition of the PD-1/PD-L1 checkpoint has led to improved patient outcomes in oncology.[198]

PD-L1 expression appears divergent in different forms of vascular inflammation with downregulation in LVV and overexpression in atherosclerosis.[199] In LVV, this downregulation allows unopposed T-cell activation and leads to the classic florid inflammatory response.[200] In atherosclerosis, sustained PD-L1 overexpression appears to impair T-cell activation and clonal expansion, which normally have protective roles in response to plaque inflammation.[201] PET tracers that bind to PD-1/PD-L1 and report its activity to guide anticancer therapy

have now been evaluated in clinical studies with encouraging results.[202,203] With further development, scientists may be able to precisely and noninvasively define the nature of vessel inflammation and monitor response to treatment through so-called immuno-PET. Further detailed characterization of these pathways, including changes after treatment, is necessary, but PD-1/PD-L1 targeting offers an exciting novel imaging and therapeutic frontier in vasculitis.

Conclusions

Major advances in the management of systemic vasculitis have taken place over the last decade. Advances in pathogenesis and imaging technology have translated into safer, more effective treatments and less invasive diagnostic and monitoring methods. Despite the success of blocking IL-6 and T-cell activation in GCA, relapse rates and glucocorticoid use remain high suggesting further refinement is needed. This is particularly true for TA where these novel agents appear to offer little benefit. The discovery of mutations in ADA2 in familial PAN syndromes may yield further insights into classical PAN and treatment options including TNFα blockade. ANCA-associated vasculitis has seen landmark improvements in clinical outcomes by targeting B cells. Recent trials of therapies that target B-cell activation, complement and IL-5 provide encouraging evidence of better outcomes for these patients. In addition, imaging has emerged to take a central role in vasculitis with ultrasound, CT, MRA, and PET each demonstrating unique strengths and limitations for diagnosis of LVV. Robust imaging-based methods of assessing disease activity remain elusive because of a discordance with clinical biomarkers, lack of comparable histology in many cases, and confounding by atherosclerosis. The advent of novel tracers and immuno-PET that allow noninvasive tracking of immune checkpoint activity may provide a solution. Further refinement of both treatments and imaging technology will hopefully allow clinicians to offer patients with vasculitis noninvasive disease monitoring, more precise treatments, and truly individualized patient management in the near term.

Sources of Funding

T.E. Farrah is supported by a Medical Research Council Clinical Research Training Fellowship.

Disclosures

None.

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Highlights

- The emergence of novel biologics such as abatacept, tocilizumab, and ustekinumab offers more precise targeting of the immune response in large vessel vasculitis and has shown promise in minimizing glucocorticoid reliance.
- Novel therapies for B-cell targeting in antineutrophil cytoplasmic antibody–associated vasculitis aim to build on the success of rituximab. Complement blockade has shown promise in preclinical studies and recent clinical trials while mepolizumab demonstrates the key role of interleukin-5 in eosinophilic granulomatosis with polyangiitis.
- Multimodal imaging including positron emission tomography with computed tomography and magnetic resonance has proven utility in diagnosis of large vessel vasculitis. The role of positron emission tomography in tracking disease activity is highly promising but needs greater refinement.
- Immuno-positron emission tomography and retinal optical coherence tomography may be the next generation of imaging modalities to offer noninvasive assessment and monitoring of systemic vasculitis.